Lucy Fraiser Toxicology Consulting LLC

Memorandum

To: Eric Sisk, Midwest Sterilization Corporation (MSC)

CC:

From: Lucy Fraiser, PhD, DABT

Date: June 24, 2020

Re: Comments on Uncertainty in Ethylene Oxide (EtO) Science and Risk Assessment Methods

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This memorandum responds to your request for comments on the uncertainty in ethylene oxide (EtO) science.

Introduction

The purpose of characterizing risk to inform rulemaking under the Clean Air Act (CAA) is to determine whether emission standards based on emission control technologies, work practices, and other control measures available are adequate to protect public health.

The specific language (section 112(f)(2)(A)) in the Clean Air Act requires that EPA set additional standards if they determine that the Maximum Achievable Control Technology (MACT) standards do not reduce the lifetime excess cancer risks to the most exposed individual to less than 1-in-one million. In controlling risks with an "adequate margin of safety", EPA strives to limit persons living near a plant to an excess cancer risk of 100-in-one million or less, assuming the individual is continuously exposed (24 hours/day, 7 days/week) to the maximum pollutant concentrations for 70 years." (FR 38044, Sept. 14).

Although this introductory information need not be included in the comments being prepared, these presumptive risk acceptability thresholds are important to understanding how risk assessment results based on the 2016 EtO cancer potency factor may be used in revising emission standards for sterilization facilities and why this approach is not appropriate for setting EtO standards.

Weaknesses in Scientific Evidence on EtO Carcinogenicity

It makes no sense to use risk assessment results to develop regulations for the purpose of protecting public health without considering the strengths and weaknesses of the evidence implicating a pollutant as a risk driver.

A false narrative about the dangers of EtO is being perpetuated by misconceptions about the evolving EtO science and risk assessment methods. The recent regulatory focus on EtO came on the heels of the National Air Toxics Assessment (NATA) released by EPA in August of 2018. The NATA concluded that EtO emissions from sterilization and chemical plants may cause elevated cancer risks in surrounding communities. These elevated cancer risks were the direct result of a 30-fold increase in EPA's *modeled hypothetical* cancer potency factor (published in 2016) [1], which was used to estimate risk in the NATA, not any evidence of increased emissions or new scientific data showing EtO to be a more potent carcinogen. In fact, according to the 2014 National Emissions Inventory technical support document,[2] emissions of EtO are down substantially from 2011. Moreover, EPA's 2016 cancer potency estimate is based on the same worker studies, involving exposures spanning the period from 1938 to 1986,[3] used to support previous, less stringent EtO cancer potency factors.[4] However, the science and risk

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[1] EPA, 2016. Evaluation of the inhalation carcinogenicity of ethylene oxide (CASRN 75-21-8): In support of summary information on the integrated risk information system (IRIS). EPA/635/R-16/350Fa. December 2016. National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington, D.C. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1025.

[2] EPA, 2018. 2014 National Emissions Inventory, version 2 Technical Support Document. Office of Air Quality Planning and Standards Air Quality Assessment Division, Emissions Inventory and Analysis Group, Research Triangle Park, North Carolina. See Table 2-8.

[3] Steenland, K; Stayner, L; Deddens, J. 2004. Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: Follow up extended from 1987 to 1998. *Occup Environ Med*, 61(1): 2-7. https://oem.bmj.com/content/61/1/2.long; Steenland, K, Whelan, E, Deddens, J, Stayner, L, Ward, E. 2003. Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). *Cancer Causes Control*, 14:531-539. https://link.springer.com/article/10.1023/A:1024891529592.

[4] EPA, 2011. Evaluation of the inhalation carcinogenicity of ethylene oxide (CASRN 75-21-8): In support of summary information on the integrated risk information system (IRIS). EPA/600/P-03/007B. July 2011. National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington, D.C. https://nepis.epa.gov/Exe/ZyNET.exe/P100LWRO.TXT?ZyActionD=ZyDocument&Client=EPA&Index=2011+Thru+2015&Docs=&Query=&Time=&EndTime=&SearchMethod=1&TocRestrict=n&Toc=&TocEntry=&QField=&QFieldYear=&QFieldMonth=&QFieldDay=&IntQFieldOp=0&ExtQFieldOp=0&XmlQuery=&File=D%3A%5Czyfiles%5CIndex%20Data%5C11thru15%5CTxt%5C00000014%5CP100LWRO.txt&User=ANONYMOUS&Password=anonymous&SortMethod=h%7C-&MaximumDocuments=1&FuzzyDegree=0&ImageQuality=r75g8/r75g8/x150y150g16/i425&Display=hpfr&DefSeekPage=x&SearchBack=ZyActionL&Back=ZyActionS&BackDesc=Results%20page&MaximumPages=1&ZyEntry=1&SeekPage=x&ZyPURL; EPA, 2006. Evaluation of the Carcinogenicity of Ethylene Oxide. *External Review Draft.* EPA/635/R-06/003. August 2006. National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington, D.C.

assessment methods used to develop the 2016 cancer potency factor for EtO are the subject of considerable controversy, as discussed below.

Uncertainty about the Carcinogenicity of EtO

Although the 2016 cancer potency factor for EtO is one of the highest inhalation unit risk factors published,[5] EPA concluded that the human evidence of EtO carcinogenicity was strong but inconclusive,[6] while the International Agency for Research on Cancer[7] determined that the human evidence was limited.

Although the 2016 EtO cancer potency assessment concludes that most human studies of the relationship between occupational exposure to EtO and cancer suggest a possible increased risk of lymphohematopoietic cancers and female breast cancer, the epidemiology evidence is inconsistent, despite occupational exposures to EtO concentrations that were thousands to millions of times higher than environmentally-relevant levels (i.e., those currently found in air). Contrary to EPA claims, most of the studies fail to support statistically significant associations between EtO exposure and cancer. Of the eight EtO lymphohematopoietic cancer studies identified in Table 3-1 of EPA's 2016 cancer potency assessment,[8] most report that the risk of lymphohematopoietic cancer is not statistically significantly elevated (i.e., many standardized incidence ratios [SIR] and standardized mortality ratios [SMR] are < 1 and most of the confidence intervals include 1, indicating a lack of statistical significance). Similarly, as shown in Table 3-2 of EPA's 2016 cancer potency assessment, the six individual EtO breast cancer studies each report that the risk of breast cancer is not statistically significantly elevated (i.e., most SIR/SMR are < 1 and the confidence intervals all include 1). Therefore, despite EPA's claims, the evidence fails to demonstrate clear or consistent associations between occupational exposure to EtO and breast or lymphohematopoietic cancer, despite the fact that worker cohorts were exposed to high concentrations of EtO over relatively lengthy periods of time in a variety of workplace settings.

It is important to keep in mind that there are no human data to inform cancer risk estimates at low environmentally-relevant EtO concentrations (i.e., those levels found in ambient air). However, even in the National Institute for Occupational Safety and Health (NIOSH) cohort used to estimate the 2016 EtO cancer potency factor, which was exposed to very high

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[5] Regional Screening Levels at https://www.epa.gov/risk/regional-screening-levels-rsls-generic-tables; Vincent MJ, Kozal JS, Thompson WJ, Maier A, Dotson GS, *et al.*, 2019. Ethylene oxide: cancer evidence integration and dose-response implications. *Dose Response* 17(4): 1559325819888317. https://doi.org/10.1177/1559325819888317.

[6] https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1025.

[7] IARC, 2008. International Agency for Research on Cancer. 1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide). *IARC Mono Eval Carcinog Risks Hum*, 97: 185 – 288. https://publications.iarc.fr/115.

[8] EPA, 2016. Evaluation of the inhalation carcinogenicity of ethylene oxide (CASRN 75-21-8): In support of summary information on the integrated risk information system (IRIS). EPA/635/R-16/350Fa. December 2016. National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington, D.C. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1025.

concentrations of EtO, for decades in some cases, the dose-response relationship between cumulative EtO exposure and lymphohematopoietic cancer was mostly only observed in males, and the magnitude of the effect was not large. A systematic literature review and meta-analysis of studies of lymphohematopoietic and breast cancer risk in workers exposed to EtO[9] concluded that more recent studies (published in the 2000s and 2010s), which involved lower EtO exposures, do not support an association between EtO exposure and increased risk of lymphohematopoietic or breast cancer. A focused review of the epidemiological and toxicological evidence[10] on EtO carcinogenicity identified in EPA's 2016 EtO cancer potency review concluded that studies identified by the authors as being of high and medium quality generally did not find statistically significant associations between EtO and cancer. Finally, the Texas Commission on Environmental Quality (TCEQ)[11] performed a carcinogenic dose-response assessment and derived an inhalation unit risk factor for EtO and concluded that, while the evidence suggested a potential association between EtO and human lymphohematopoietic tumors, the epidemiological evidence for EtO-induced human breast cancer is very weak.

Uncertainty about the Potency of EtO as a Carcinogen

The TCEQ derived a cancer potency factor that was a small fraction of EPA's (i.e., 0.00046 or < 0.05%) using two high-exposure occupational cohorts (i.e., the Union Carbide Corporation [UCC] and NIOSH cohorts)[12] and a different dose-response model from EPA (i.e., Cox

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[9] Marsh GM, Keeton KA, Riordan AS, Best EA, Benson SM. 2019. Ethylene oxide and risk of lympho-hematopoietic cancer and breast cancer: a systematic literature review and meta-analysis. Int Arch Occup Environ Health 92(7):919–939. https://doi.org/10.1007/s00420-019-01438-z.

[10] Vincent MJ, Kozal JS, Thompson WJ, Maier A, Dotson GS, *et al.*, 2019. Ethylene oxide: cancer evidence integration and dose-response implications. *Dose Response* 17(4): 1559325819888317. https://doi.org/10.1177/1559325819888317.

[11] TCEQ, 2020. Texas Commission on Environmental Quality. Ethylene Oxide Carcinogenic Dose-Response Assessment CAS Registry Number: 75-21-8. Development Support Document Final. May 15, 2020. https://www.tceq.texas.gov/toxicology/dsd/final#e.

[12] Steenland, K; Stayner, L; Deddens, J. 2004. Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: Follow up extended from 1987 to 1998. *Occup Environ Med*, 61(1): 2-7. https://oem.bmj.com/content/61/1/2.long; Steenland, K, Whelan, E, Deddens, J, Stayner, L, Ward, E. 2003. Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). *Cancer Causes Control*, 14:531-539; Greenberg, H, Ott., M, Shore, R. 1990. Men assigned to ethylene oxide production or other ethylene oxide related chemical manufacturing: a mortality study. British Journal of Industrial Medicine. 47:221-230. https://scholar.google.com/scholar?hl=en&as_sdt=0%2C4&q=Greenberg%2C+H%2C+Ott.%2C+M%2C+Shore%2C+R.+1990.+Men+assigned+to+ethylene+oxide+production+or+other+ethylene+oxide+related+chemical+manufacturing%3A+a+mortality+study.+British+Journal+of+Industrial+Medicine.+47%3A221-230.&btnG=; Swaen, G, Burns, C, Teta, J, Bodnar, K, Keenan, D, Bodnar, C. 2009. Mortality study update of ethylene oxide workers in chemical manufacturing: a 15-year update. JOEM. 51(6):714-723. https://journals.lww.com/joem/Abstract/2009/06000/Mortality_Study_Update_of_Ethylene_Oxide_Workers.11.aspx; Teta, M, Benson, L, Vitale, J. 1993. Mortality study of ethylene oxide workers in chemical manufacturing a 10-year update. British Journal of Industrial Medicine. 50:704-709. https://scholar.google.com/scholar?hl=en&as_sdt=0%2C4&q=Teta%2C+M%2C+Benson%2C+L%2C+Vitale%2C+J.+1993.+Mortality+study+of+ethylene+oxide+workers+in+chemical+manufacturing+a+1

proportional hazards model vs EPA's 2-piece spline supra-linear model). The TCEQ's cancer potency factor equates to an acceptable ambient EtO concentration[13] of 0.043 μg/m^3 vs EPA's acceptable concentration of 0.0002 μg/m^3,[14] which is 100-times more stringent (i.e., lower). Even EPA[15] acknowledges that if all combinations of potential models for both lymphohematopoietic and breast cancer are considered, estimated risks from EtO exposure could range from essentially the same to one-fifth (i.e., 20%) of EPA's 2016 cancer potency estimate.

Another difference between EPA's 2016 cancer potency factor for EtO and the one developed by the TCEQ is that EPA only used the NIOSH cohort in deriving its 2016 cancer potency factor. EPA states that it selected the NIOSH cohort because it is the study in which the evidence of lymphohematopoietic cancer is strongest and that appears to have the fewest limitations.[16] However, the direction of a study's results (i.e., positive or negative in supporting the investigator's underlying hypothesis) should not be part of the criteria used in selecting whether a study is appropriate for use in quantitatively estimating its cancer potency. If only those studies showing a positive relationship between exposure and cancer are used to estimate cancer potency, cancer risk will almost certainly be overstated.

EPA's exclusion of the UCC data (the other occupational study included by the TCEQ), which failed to support a positive association between EtO exposure and lymphohematopoietic or breast cancer, was based on EPA's conclusion that the exposure assessment was much cruder than the NIOSH exposure assessment, which EPA claims was based on a validated regression model. However, Bogen and colleagues (2019)[17] investigated the regression model used in the NIOSH study to estimate EtO exposure concentrations during years when EtO exposure

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0+year+update.+British+Journal+of+Industrial+Medicine.+50%3A704-709.&btnG=; Teta, J, Sielken Jr, R, Valdez-Flores, C. 1999. Ethylene oxide cancer risk assessment based on epidemiological data application of revised regulatory guidelines. Risk Analysis. 19(6):1135-1155. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1539-6924.1999.tb01134.x.

[13] TCEQ uses a target cancer risk of 1-in-100,000 but for comparing to EPA's standard acceptable air concentration for carcinogens, a target cancer risk of 1-in-1,000,000 was used here.

[14] Based on acceptable cancer risk of 1-in-1,000,000.

[15] EPA, 2019. Memorandum from Kristina Thayer to Peter Tsirigotis on October 8, 2019 entitled IRIS EtO Assessment - Modeling Comparison and Assessment of Uncertainty.

[16] EPA, 2016. Evaluation of the inhalation carcinogenicity of ethylene oxide (CASRN 75-21-8): In support of summary information on the integrated risk information system (IRIS). EPA/635/R-16/350Fa. December 2016. National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington, D.C. p. 3-12. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1025.

[17] Bogen, KR, Sheehan, PJ, Valdez-Flores, C, Li, AA, 2019. Reevaluation of Historical Exposures to Ethylene Oxide Among U.S. Sterilization Workers in the National Institute of Occupational Safety and Health (NIOSH) Study Cohort. Int J Environ Res Public Health, 16: 1738. https://scholar.google.com/scholar?hl=en&as_sdt=0%2C4&q=Bogen%2C+KR%2C+Sheehan%2C+PJ%2C+Valdez-Flores%2C+C%2C+Li%2C+AA%2C+2019.+Reevaluation+of+Historical+Exposures+to+Ethylene+Oxide+Among+U.S.+Sterilization+Workers+in+the+National+Institute+of+Occupational+Safety+and+Health+%28NIOSH%29+Study+Cohort.+Int+J+Environ+Res+Public+Health%2C+16%3A+1738.+&btnG=.

data were not available for the cohort (i.e., all years before 1978) by comparing the predicted concentrations to measurements from worker personal breathing zones[18] in 18 sterilization facilities (13 facilities were represented in the NIOSH cohort). These investigators found that by using only the NIOSH cohort, EPA underestimated EtO exposure concentrations during the early years (by a factor of more than 10-fold),[19] which had the effect of overestimating EtO cancer potency. In view of the uncertainty raised by these investigators about the predicted historical EtO exposures of sterilization workers, EPA's exclusive reliance on the NIOSH cohort to estimate EtO cancer potency and risk should be re-examined.

One justification frequently used as a reason for excluding the results of other studies in estimating the cancer potency of EtO was small cohort size. However, instead of excluding small studies from consideration, meta-analysis could have been used to critically evaluate and statistically combine the results of both positive and negative results from large and small studies. This would have increased the numbers of observations, boosted statistical power, and improved the estimates of the effect size. One meta-analysis of studies of lymphohematopoietic and breast cancer risk in workers exposed to EtO (discussed previously)[20] demonstrated that studies published after the year 2000 reported lower relative risks for lymphohematopoietic cancer than those published in the 1980s and 1990s.

Impracticality of Using the 2016 EtO Cancer Potency Factor to Identify Unsafe Levels in Air

The 2016 EtO cancer potency factor is neither reasonable as a health standard, nor is it useful for identifying unsafe levels of EtO in the ambient air because it corresponds to concentrations of EtO in air (i.e., 0.0002 to 0.02 $\mu g/m^3$) that are lower than the level that can currently be measured (i.e., 0.04 $\mu g/m^3$). These "acceptable" concentrations are also well below levels of EtO found in ambient air across the country based on monitoring conducted by EPA in areas not impacted by emissions from sterilization plants. These monitoring results indicate that existing background levels of EtO are between 0.2 and 0.4 $\mu g/m^3$.[21]

Regulation of EtO emissions needs to consider the context of the world in which we live. Given that EtO is emitted from a wide variety of sources other than sterilization plants, further regulation of emissions from sterilization facilities is unlikely to substantially affect existing

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[18] Mostly collected between 1978 and 1985.

[19] The EPA model showed an increasing trend in predicted EtO levels during the 1938–1978 time frame, despite the fact that it was well recognized by others at NIOSH that before the late 1970s, EtO exposures among sterilizer workers "were likely to have been higher because this was before installation of engineering controls, when the OSHA standard was 50 ppm. The model results from Bogen *et al.*, 2019 for medical/health product sterilization showed an overall decreasing historical trend in estimated concentrations during the period 1938–1978, with exposures in the early period higher than in 1978. EPA's model essentially assumed that there were no substantive changes in sterilization operations before 1978.

[20] Marsh GM, Keeton KA, Riordan AS, Best EA, Benson SM. 2019. Ethylene oxide and risk of lympho-hematopoietic cancer and breast cancer: a systematic literature review and meta-analysis. Int Arch Occup Environ Health 92(7):919–939. https://doi.org/10.1007/s00420-019-01438-z.

[21] https://www.epa.gov/hazardous-air-pollutants-ethylene-oxide/ethylene-oxide-updates.

background EtO concentrations that are already higher than EPA-sanctioned "acceptable" levels in areas distant from the sterilization facilities. Therefore, it is not possible to set standards for EtO emissions from sterilization plants that will reduce ambient concentrations to the levels dictated by the 2016 cancer potency factor. Even if such a standard could be set, it would be impossible to confirm that risks had been reduced to an acceptable level because there are no currently available EtO analytical methods capable of measuring levels ranging from 0.0002 to 0.02 $\mu g/m^3$.

Conclusions

As discussed above, and acknowledged by both EPA and IARC, human data by itself does not provide consistent or conclusive evidence that EtO is a human carcinogen. Importantly, the toxicological evidence is also generally unsupportive of EtO's carcinogenicity, as many of those studies fail to confirm a positive association between EtO exposure and carcinogenicity as well.[22] The overall body of scientific evidence fails to support that lymphohematopoietic or breast cancer risks are significantly elevated in workers exposed to historically high EtO exposure concentrations, much less in the general population, which is exposed to EtO levels in ambient air that are a tiny fraction (i.e., 0.001 or < 0.1%) of historically high occupational levels. Given that the epidemiological evidence is largely negative (including the NIOSH studies), a proper risk assessment cannot be based on these epidemiological studies. Therefore, derivation of the 2016 cancer potency factor for EtO using a 2-piece, supra-linear dose–response model, which resulted in one of the highest cancer potency estimates published, does not appear to have been adequately justified based on the published literature.

In view of the uncertainty about whether current day EtO levels can cause cancer in humans, the uncertainty that alternative modeling analyses raise about predictions of historical worker EtO exposures from the NIOSH studies, and EPA's exclusive reliance on the NIOSH cohort in deriving the 2016 EtO cancer potency factor, further regulation of EtO emissions from sterilization plants based on the EtO cancer potency factor plants should be reconsidered.

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[22] Vincent MJ, Kozal JS, Thompson WJ, Maier A, Dotson GS, *et al.*, 2019. Ethylene oxide: cancer evidence integration and dose-response implications. *Dose Response* 17(4): 1559325819888317. https://doi.org/10.1177/1559325819888317.